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RESEARCH ARTICLE

Formulation Development of Eudragit Coated Polymeric Matrices for Targeted and Controlled Delivery to the Colon

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ABSTRACT

Colon targeted release tablets containing 25-75mg of indomethacin were formulated using Eudragit Coated Polymeric Matrices. Nine batches of indomethacin tablets were prepared containing varying concentrations of Eudragit-S100 (E-S100, 0.94-37.56% w/w), mucin (43.82- 87% w/w), sodium caboxymethyl cellulose (NaCMC, 3-5% w/w) and microcrystalline cellulose (MCC, 9.39% w/w). Batches I-VII granules were prepared using non-aqueous or aqueous/non-aqueous wet granulation methods while batches VIII-IX granules were prepared by dry granulation method. Batches IV-IX tablets were coated with E-S100 or a mixture of E-S100 and Eudragit-L100 to between 4-8% of the tablet weight. Sequential dissolution studies were carried out on the coated tablets in buffer solutions of pH 1.2, 6.8 and 7.2 for 15 hours. Results showed that all the granule samples were compressible except Batch III containing 37.56% w/w of E-S100. Batches VIII and IX Indomethacin tablets coated with 3.76-4.47% w/w of E-S100 exhibited dissolution profiles potentially promising for targeted colonic drug delivery.

KEYWORDS

Targeted Colonic Drug Delivery, Coated Polymeric Devices, Indomethacin

INTRODUCTION

The oral route is considered to be most convenient for the administration of drugs to patients. Site specific drug delivery to the colon has gained increasing importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon but also as potential site for the systemic delivery of therapeutic peptides and proteins.[1-4] Orally administered conventional dosage forms normally dissolve in the gastric fluid or intestinal fluid and absorption from these regions of the gastrointestinal tract (GIT) depends upon the physicochemical properties of the drug.

It is a serious drawback in conditions where localized delivery of the drugs in the colon is required or in conditions where a drug needs to be protected from the hostile environment of upper GIT.

Therefore, per oral colonic drug delivery is very important in these conditions since it poses a lot of advantages.

So, development of coated matrices for targeted and controlled delivery to the colon using

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poorly soluble active pharmaceutical ingredients like indomethacin is important because the delivery of highly soluble and poorly absorbed drugs to the colon could also be optimised from such matrices.[5]

MATERIALS AND METHODS

Materials

Porcine mucin (locally produced), microcrystalline cellulose pH 101 (Ruka AG. Chem. Fabrik, China), eudragit-S100 and eudragit L100 (free gift from Rohm Pharmaceuticals, Germany), hydroxyethyl cellulose (Fluka, Germany), magnesium stearate (TreePac Laboratories, Germany), talc (Jawa Pharm., Nigeria), sodium carboxymethyl cellulose-type 7HF (Merck, NJ, USA), distilled water (Lion Water, UNN, Nigeria), sodium chloride (Merck, Germany), hydrochloric acid (BDH, England), potassium dihydrogen orthophosphate (BDH, England), sodium hydroxide (Merck, Germany), isopropanol (Merck, Germany), aerosil (Evonik, Germany), ethanol (BDH, England), methanol (Sigma Aldrich, Germany).

Methods

Assay of Indomethacin

The method described in USP (2004) was used to assay for the purity of indomethacin.[6]

Formulation and Evaluation of Batches I-V Tablets

Batches 1-5 tablets were prepared by non-aqueous wet granulation method using the formula shown in table-1 below. The crushing strengths of the tablets were determined with a Monsanto hardness tester. Because of the better compressibility and hardness test results of tablets of Batches IV & V, they were further film coated and the hydromechanical strength of the film coatings evaluated in relation to the mucin/eudragit-S100 content ratios of the coated tablet matrix.

Coating of Batches IV and V Tablets

A 10% w/v solution of eudragit-S100 in ethanol: water mixture (6:4$^{v}/_{v}$) was used to coat the tablets by dip method. The tablets were coated up to 13%$^{w}/_{w}$ (of core matrix) after about four dips in the coating mixture.

Table 1: Formula for Preparation of Batches I-VII Indomethacin Tablets

Ingredients	Quantity (%)						
	I	II	III	IV	V	VI	VII
Indomethacin	7.82	7.82	7.82	7.82	7.82	8.3	8.3
Eudragit-S100	0.94	4.69	37.56	5	10	-	5
Mucin	80.44	76.68	43.82	76.38	71.38	3	5
MCC	9.39	9.39	9.39	9.39	9.39	-	-
NaCMC	-	-	-	-	-	87	80
Mg. St.	0.47	0.47	0.47	0.47	0.47	0.3	0.3
Talc	0.94	0.94	0.94	0.94	0.94	1.4	1.4

MCC=Microcrystalline Cellulose, Mg. St. = Magnesium Stearate, NaCMC = Sodium Carboxymethylcellulose

Determination of the pH-Dependent Hydromechanical Strength of the Coating Film

The ability of the coating film to prevent disintegration in aqueous media was determined by performing a sequential disintegration test on the coated tablets in three buffer solutions of pH 1.2, 6.8 and 7.2 in increasing order of sequence. The experiment above was done using an Erweka disintegration unit. The buffered solutions were maintained at a temperature of 37±1°C and the disintegration unit operated at a frequency of about 32 cycles per minute. The rate/extent of coating film collapse was determined by measuring the time of rupture and length of the rupture slit at predetermined time intervals. From the results of experiments above, there was a need to retard the bulk release of indomethacin and so, the MCC (a wicking agent) was replaced with NaCMC (a swellable hydrophilic polymer), giving rise to Batches VI & VII.

Preparation of Batches VI & VII Indomethacin Tablets

The Batch-VI tablets were prepared by aqueous wet granulation method while batch-VII tablets were prepared using a combined aqueous/non-aqueous wet granulation method[7] employing the formula in Table-I above.

Coating of Batches VI and VII Indomethacin Tablets

The tablets of Batches VI & VII were then coated with an 8% w/v solution of a binary mixture of eudragit-S100: eudragit-L100 (1:1 w/w) in ethanol. The tablets were impacted an average coating film of 8.03±0.0.9211% w/w of the core matrix by dip method.

Dissolution of Coated Batches VI and VII Indomethacin Tablets

A sequential dissolution of the coated tablets was done in buffer solutions at three pH levels of 1.2 (for 2hours), 6.8 (for 3-4hours) & 7.2 (for 10hours) at a temperature of 37 ± 1°C, by employing the USP Method-II (paddle method)[8] using an Erweka dissolution apparatus, at a paddle rotation speed of 50rpm. The samples generated were assayed using the UV-VIS spectrophotometer at a λ_{max} = 320nm.

Preparation of Batches VIII and IX Indomethacin Tablets by Dry Granulation

Because of the poor release of indomethacin (a hydrophobic and poorly soluble drug) which could be a consequence of the wet granulation method adopted in the formulation of previous tablets, the dry granulation technique[7] with some modifications in the formulation as shown in Table-2 below was used in the preparation of batches VIII and IX tablets.

Table 2: Formula for Preparation of Batches VIII and IX Indomethacin Tablets (By Dry Granulation)

Ingredients	Quantity (%)	
	VIII	IX
Indomethacin	25.17	17.05
HEC	67.11	68.18
Eudragit-S100	6.71	13.64
Aerosil	0.5	0.57
Magnesium Stearate	0.5	0.57

HEC = Hydroxyethylcellulose

Coating of Batches VIII and IX Tablets

The tablets were coated with eudragit S100 (in an admixture of propylene glycol, water and isopropyl alcohol) using an adjusted coating pan method.[9]

The tablets were impacted different coating levels of 3.76% w/w (for batch-VIII only) and 4.47% w/w (for batches VIII & IX).

Drug Release Studies of Coated and Uncoated Batches VIII and IX Indomethacin Tablets

The dissolution of the uncoated indomethacin tablets were performed in phosphate buffer solution of pH 7.2 for 2–3hours. But for the coated tablets, the release profiles were

sequentially determined in three buffer solutions of pH 1.2 (for 2hours), 6.8 (for 3hours) & 7.2 (for 10hours). The samples from dissolution studies were spectrophotometrically analyzed at a λ_{max} =318nm.[10]

RESULTS AND DISCUSSION

Crushing Strengths of Batches 1 – V Indomethacin Tablets

Results have shown that wet granulated powders containing up to 37% of eudragit S100 are not compressible into tablets but 5 – 10% w/w of eudragit S100 has proved to be the optimum concentration for wet granulated tablets in terms of compressibility and tablet hardness.[11]

Table 3: Crushing Strengths of Batches I – V Indomethacin Tablets

Batch	I	II	III	IV	V
Hardness (kgf)	≤ 2	3 – 3.5	< 1	4.7±0.1	5.15±0.65

n =5

Hydromechanical Strength of the Eudragit-S100 Coating Film of Batches IV & V Tablets

The hydromechanical strength of the eudragit S100 coating film of batches IV and V tablets is shown in Table-4 below. The result shows that increase in the concentration of eudragit-S100 in the tablet matrix causes an increase in the time of rupture and a decrease in the length of rupture of the coating film.

This is because, eudrgit-S100 is hydrophobic and so, it will attract less aqueous medium into the tablet matrix, consequently, preventing a substantial swelling of the polymeric materials contained in the tablet.[12] The swelling, in no small measure contributes to the breaking up or collapse of the coating film.

Thus, it is important to note that apart from the coating film thickness, the nature (e.g. water sorption capacity) of the materials in the tablet matrix contributes to the strength and collapse or cracking of the coating film in dissolution medium.

Table 4: Effect of pH and Hydraulic Pressure on the Coating Film of Batches IV and V Tablets

Batch	Effect of pH and Hydraulic Pressure on Coating Film		
	pH 2	pH 6.8	pH 7.2
IV	The tablet ruptured and disintegrated in less than 20mins remaining only the coating film.	A new tablet (coated) was used. The tablet coating film cracked after 3Hours with a slit length of 0.7 – 0.8cm on the tablet circumference.	After 2hrs 40mins, about 50 – 60% of the coating film was cracked and opened up the tablet matrix, thereby, exposing greater percentage of the matrix.
V	There was no crack on the coating film after 20mins and above.	The coating film cracked after 3hours with a slit length of 0.7 – 0.8cm on the tablet circumference.	The crack on the coating film was extended almost to the centre segment of the tablet.

In Vitro Drug Release Characteristics of Coated Batches VI and VII Indomethacin Tablets

Indomethacin tablets from batches VI and VII could not deliver significant quantities of indomethacin in the colonic environment but released only 16.67% and 13.26% of indomethacin contents respectively, after 15hours of sequential dissolution study. The poor drug release notwithstanding, the dissolution profiles have interesting patterns and kinetics as shown in Figure 1.

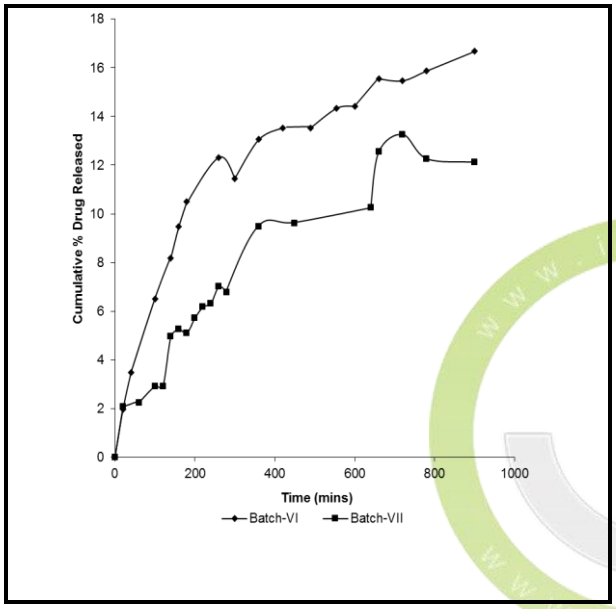

Figure 1: Sequential Dissolution of 8.03%Coated Indomethacin Tablets (Batches VI & VII) in Aqueous Media of pH 1.2, 6.8 and 7.2

Crushing Strengths of Uncoated Batches VIII and IX Indomethacin Tablets

Using the Monsanto hardness tester, the crushing strengths of the uncoated batches VIII and IX tablets were within 8 ± 0.2kgf. This is desirable for a targeted sustained release product of this nature.

In Vitro Drug Release Characteristics of Coated and Uncoated Batches VIII and IX Indomethacin Tablets

The drug release from uncoated batches VIII and IX tablets in aqueous medium of pH 7.2 was up to 50 – 60 % of indomethacin within 2hours which gives an insight that the drug could be substantially released from the tablets in the colonic environment.

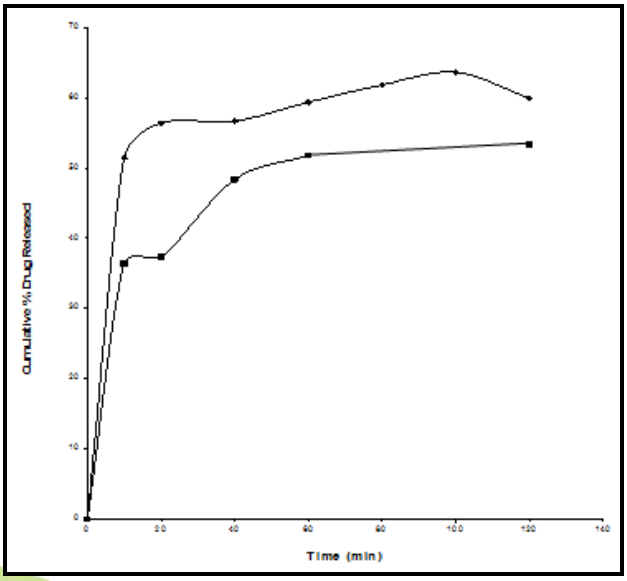

Figure 2: Release of Indomethacin from Uncoated Batches VIII and IX Tablets in Aqueous Medium of pH 7.2

The sequential dissolution result of the 3.76%coated batch-VIII Indomethacin tablets in three aqueous media of pH 1.2, 6.8 and 7.2 are shown in Figure 3. The dissolution profile displayed a sigmoid shape. During the lag phase, the coated tablets released up to 10.48% of the stated content of indomethacin after 300minutes (5hours) and thereafter, released up to 24.28% of the stated content of indomethacin after 600 mins (10hours) in simulated colonic fluid (SCF) of pH 7.2. This increase in cumulative percentage released of indomethacin in the SCF could be attributed to the dry granulation technique applied which may not allow encapsulation of the poorly soluble indomethacin molecules and so, improving release.

The sequential dissolution profiles of 4.47%coated Batches VIII and IX tablets are represented in Figure 11 and Figure 12. The tablets showed total drug releases of up to 5.6385% and 8.4228% of indomethacin content respectively after 300minutes in simulated gastric and intestinal fluids of pH 1.2 and 6.8 respectively. But, when the coated tablets were

transferred to SCF of pH 7.2, there were drug releases up to 21.577% and 21.093% of indomethacin respectively. There was virtually no significant difference in the percentage of drug released between the two batches in the SCF notwithstanding the difference in the content of E-S100 between the two batches. These sequential dissolution results for Batches VIII and IX coated tablets were remarkable for targeted and controlled delivery of practically insoluble indomethacin to the colon.

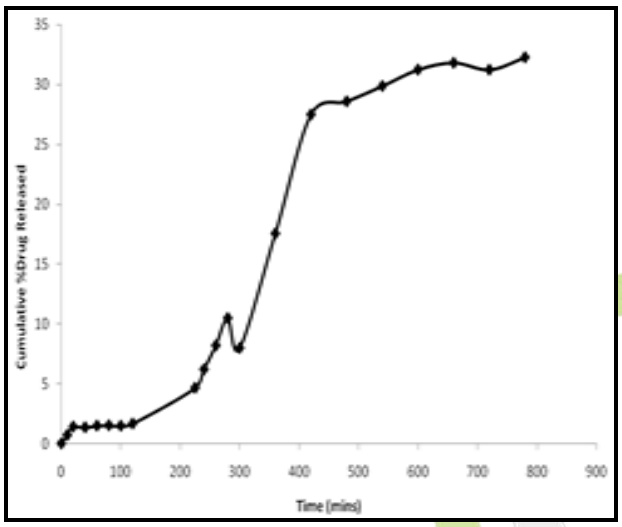

Figure 3: Sequential Release of Indomethacin from 3.76 % coated Batches VIII tablets in Aqueous Media of pH 1.2 (120 min), 6.8 (180 min) and 7.2 (420 min)

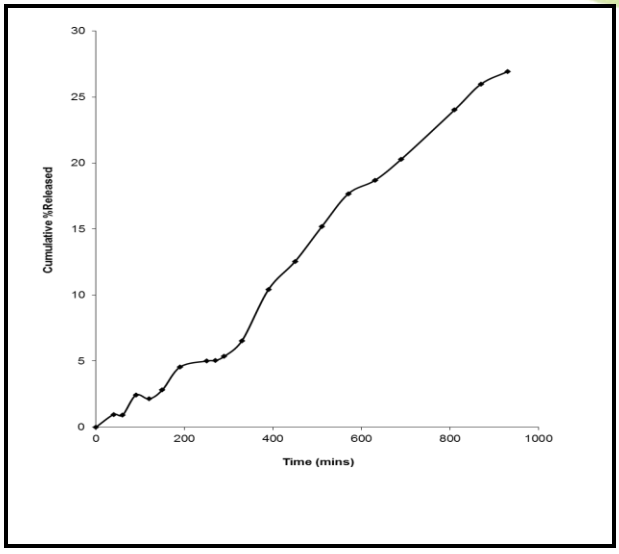

Figure 4: Sequential Release of Indomethacin from 4.47%Coated Batch-VIII Matrix Tablets in Aqueous Media of pH 1.2 (150mins), 6.8 (180mins) & 7.2 (600mins)

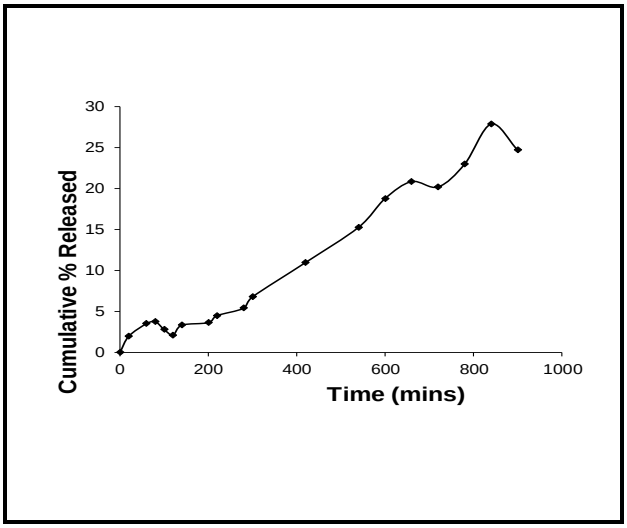

Figure 5: Sequential Release of Indomethacin from 4.47%Coated Batch-IX Tablets in Aqueous Media of pH 1.2 (120mins), 6.8 (180mins) & 7.2 (600mins)

CONCLUSION

The 3.76 – 4.47% eudragit s100 coated batches VIII and IX indomethacin tablets exhibited dissolution profiles potentially good for colon delivery and so, they could be further developed to serve as templates for the colonic delivery of other practically insoluble drugs, hydrophilic drugs, etc.

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